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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/830,779	11/30/2001	Kenneth Chien	6627-PA9025	3690

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EXAMINER	
DUFFY, PATRICIA ANN	

ART UNIT	PAPER NUMBER
1645	

DATE MAILED: 02/28/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/830,779	CHIEN ET AL.	
	Examiner	Art Unit	
	Patricia A. Duffy	1645	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *2-28-05*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,4,12,16,19,20 and 22-56* is/are pending in the application.

4a) Of the above claim(s) *24-39* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,4,12,16,19,20,22,23 and 40-56* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *2006*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

RESPONSE TO AMENDMENT

The amendment filed 2-28-05 has been entered into the record. Claims 2-3, 5-11, 13-15, 17-18 and 21 have been cancelled. Claims 1, 4, 12, 16, 19, 20 and 22-56 are pending. Claims 1, 4, 12, 16, 19, 20, 22, 23, 40-56 are under examination.

The text of Title 35 of the U.S. Code not reiterated herein can be found in the previous office action.

Lack of Unity

This application contains claims 24-39 drawn to an invention nonelected with traverse in the reply filed 3-17-03. A complete reply to the final rejection must include cancellation of nonelected claims or other appropriate action (37 CFR 1.144) See MPEP § 821.01.

Applicants argue that when making a lack of unity requirement the Office must explain why each group lacks unity of invention. Applicants argue that the protein claims and the nucleic acid claims share a special technical feature pursuant to Rule 13.1. Applicants argue that the newly drawn species should be rejoined in view of the Lack of Unity requirement set forth previously. This is not persuasive. The claims do not share the same special technical feature. The first technical feature is the dominant negative protein functionally attached to a transport peptide or a vesicle based transfer system. The second technical feature is an expression construct comprising a coding sequence for a dominant negative PLB functionally linked to a promoter active in the heart or muscle cell. As currently claimed, these are structurally distinct technical features. The methods using the nucleic acid do not require the protein functionally attached to a transport peptide. The nucleic acid does not encode the technical feature of Group I (i.e. the protein functionally attached to a transport peptide). As set forth therein, "Upon the allowance of a generic claim, applicants will be entitled to consideration of claims to additional species which are written in dependent form." There are no allowable claims at

this time. Further, the examiner explained in the Lack of Unity why the species did not relate to a single general inventive concept was set forth in the original lack of Unity and " each of the species have different chemical constructions which lack a structure feature in common (protein, nucleic acid, antibody)..." . In view of the Lack of Unity mailed 2-13-03, there being no allowable generic claim, the claims drawn to methods of using the nucleic acids were properly withdrawn and remain withdrawn for reasons set forth therein.

A complete reply to the final rejection must include cancellation of nonelected claims or other appropriate action (37 CFR 1.144) See MPEP § 821.01.

Information Disclosure Statement

The information disclosure statement filed 1-26-06 has been considered. An initialed copy is enclosed.

Rejections Withdrawn

The rejection of claims 1, 4, 12, 16, 19, 20, 22, 23 and 40-45 under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement is withdrawn in view of Applicants response.

The rejection of the claims under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention is withdrawn in view of the definition provided.

Rejections Maintained

Claims 1, 4, 12, 16, 19, 20, 22, 23, 40-56 stand rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make

and/or use the invention for reasons made of record in the office actions mailed 06-03-03 and 1-20-04.

Applicants' arguments have been considered but are not persuasive. Applicants argue that the examiner has not provided a prima facie case. This is not persuasive; the office actions of record present a plethora of reasons to doubt the enablement of the specification at the time of filing. First and foremost, the specification admits that the results with the only peptide tested in vitro were not statistically significant. Despite this adverse admission in the specification, Applicants maintain the position that one can get the claimed invention to work. Applicants reiterate the teachings of the specification and the hypothesis upon which the invention was based. The office actions of record did not question the hypothesis upon which the invention was based. The teachings of the specification on how to make the truncated and mutants has been taken into consideration, as has the state of the art. In view of the lack of statistically significant findings *in vitro*, the difficulties of administration in vivo, the state of the art at the time of filing, a proper conclusion of undue experimentation was made. Applicants appear to argue that the examiner must cite literature in order to question the enablement of the specification for the claimed method. This is not persuasive, there is no per se requirement that literature is necessary to hold a finding of undue experimentation. The position has been clearly set forth in regard to the findings of the specification and the difficulties in administering or contacting the heart with a therapeutic that is receptor-independent and would necessarily be taken up by any cell in the body. Further, in contrast to the nucleic acid, the proteins cannot make more of themselves and would be reasonably expected to have a short half-life, even if one could deliver to a sufficient number of heart cells to achieve the claimed result. The delivery is not an insignificant problem. The heart is a dense muscle and there must be a sufficient number of cells treated in order to achieve a functional alteration. The specification could not even get a statistical significant result in vitro using isolated cardiomyocytes, where clearly all the delivery variables could be

controlled. In the absence of success with isolated cells, how then can one skilled in the art reasonably predict that administration *in vivo* would be effective? Although, Applicants may have delivered one combination to an isolated cardiac myocyte in vitro, collectively there was not statistically significant result. The application must be enabled at the time of filing. Applicants have not established a correlation between the *in vitro* assay and *in vivo* results for the claimed enhanced cardiac contractility, treatment of heart failure or increasing heart activity. Applicants have not provided a correlation of in vitro assay with in vivo results for the peptide-based therapeutics. The record provides a long discourse on the differences that the skilled artisan would expect between peptide-based therapeutics and nucleic acid-based therapeutics. The statute not only provides that the specification must teach how to make, but how to use. While the specification provides how to make, it does not teach how to use for the claimed outcome as set forth in the preamble of the claims. Applicants argue that a single experiment does not negate the fact that the specification teaches how to make and use the invention. This is not persuasive. The position of the office is that mere reiteration of how to use, does not enable the skilled artisan for predictable use because the results presented in the specification clearly and unambiguously provide evidence at the time of filing that the in vitro assay did not work for the now claimed protein embodiments. The courts have held that the disclosure is insufficient when testing is necessary to determine the actual use or possible lack of use *(In re Kirk and Petrow* 153 USPQ 48 (CCPA 1967). Applicants argue that the skilled artisan could make the invention work using standard screening assays. This is not persuasive, the assay as set forth did not identify a peptide that provided for statistically significant results in vitro. No other assays for peptides are described in the specification and the correlation of the assay in the specification for the single tested embodiment has not been established by Applicants. The courts have held that "... whenever there is no disclosure of any specific starting material or of any of the conditions under which a process can be carried out undue experimentation is required;

there is a failure to meet the enablement requirement that cannot be rectified by asserting that all the disclosure related to the process is within the skill of the art. It is the specification, not the knowledge of one skilled in the art, that must supply the novel aspects of the invention in order to constitute adequate enablement." *Genetech Inc. v. Novo Nordisk A/S* 42USPQ2d 1001. It is unclear as to what screening process, not disclosed or relied upon in the specification could be used. As previously set forth, mere translocation in vitro does not provide for a statistically significant result in vitro. If the person of highest skill in this art, the inventor, cannot get the invention to work in vitro, how can one expect the generally skilled artisan to select *in vitro* assays not disclosed or assays that have not been established to correlate with *in vivo* efficacy as set forth in the preamble. The examiner has appropriately weighed the evidence that establishes what was known and what was not know at the time of filing. Applicants reiterate the declaration of Dr. Chien. Dr. Chien's declaration has been thoroughly considered on the record, but is not persuasive for all the reasons set forth in the last office action. Applicants argue use of penatrin peptides are an effective means for delivering doxorubicin through the blood brain-barrier. This is not persuasive, the document is published well after the earliest filing date in 1999 and does not establish that it was well known at the time of filing. Further, Rousselle et al taught was delivery to the brain and not therapeutic effectiveness. The claims require a specific therapeutic effect. The claims are not drawn to a method of delivery of a truncated PLB, dominant negative PLB to the heart. The relied upon art did not address the therapeutic effectiveness of the delivered molecule. Applicants reiterate the current judicial precedent with respect to enablement and reiterate that enablement is not precluded even if some experimentation is necessary. This is not persuasive, the experimentation need herein is an in vitro demonstration of effectiveness and then in vivo experimentation to determine delivery amounts, routes and repeated dosages needed to achieve the functional result of the preamble. As previously set forth, the claimed peptides are substantially hindered by

their mechanism of uptake... a receptor independent mechanism. As such, the administration of the peptide as claimed would deliver the peptide to all living cells in the body. Because of the receptor-independent uptake, their arises the complicated issue of dosaging in vivo. If all cells take up the composition, how can one deliver an amount sufficient to provide for a physiological effect ? Applicants' arguments are an invitation to the skilled artisan to further experimentation to see if one could get the claimed invention to work. Applicants again argue the declaration of Dr. Chien. Dr. Chien provides an opinion that the teachings of Example of the specification are inconclusive. This is not persuasive, Applicants' own specification discloses that the sole experiment in vitro did not provide for statistically significant results, in those words. Dr. Chien recharacterizes the experiment as inconclusive and characterize the data of the specification differently than Applicants. This is not persuasive, the same data as interpreted by Applicants, the high experts in the art, was characterized as not statistically significant. Dr. Chien relies upon the findings of the nucleic acid for enablement for the claimed polypeptide embodiment. Nucleic acids are not equivalent to the polypeptide for all the reasons already made of record. Dr. Chien asserts that different dominant negative PLB's could be discovered by the skilled artisan. This is again not persuasive, the Applicants in the specification at the time of filing must provide a description that fully supports the scope of the claimed invention. This specification does not. While the skill in the art is high, the experimentation is not routine because it is neither predictable nor reproducible. Enablement must be established in the specification at the time of filing and is to be commensurate in scope with the stated claimed. *In re Hogan and Banks*, 194 USPQ 527 (1977). To ascertain if Applicants invention was able to work, Applicants would need to develop in vitro screening assays that were predictable of the in vivo result and then move to in vivo testing. Applicants argue that testing for means of delivery is routine in the art. This is not persuasive in this case because the mode of delivery presents unusual problems such as being taken up by all cells in view of the receptor dependent mechanism, the skilled

artisan would have to discover how to specifically deliver and inherently non-specific therapeutic to the hear and then assess if it works. Such discovery is itself the act of invention, and this would require ingenuity beyond that expected by one of ordinary skill in the art. Fields v. Conover, 170 USPQ 276, 279 (CCPA 1971). Further, it is complicated by lack of demonstration of success either in vitro or in vivo of any similar transport peptide. As such, it is not merely following in the footsteps of the inventors to test other similar peptides, but requires the initial testing to see if even one would work. The record establishes using Applicant own words that the peptide in vitro did not work and the results were not statistically significant. Therefore, the experimentation would be beyond the skill of the artisan and therefore undue.

The rejection is maintained.

Claims 1, 4, 12, 16, 19, 20, 22, 23, 40-42, 45-48, and 52 -56 stand rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement for reasons made of record in the Office Action mailed 12-30-04.

Applicants' arguments have been carefully considered but are not persuasive. Applicants argue other modes of receptor independent transport (i.e. adenovirus and lipid vesicle mediated). The mode of transfer is not the issue. The issue is not means of transfer, but the term "transport peptide" now including receptor-mediated peptides. The mode of transfer is NOT the issue. Support for conception of the genus of transport peptides (i.e. those that are receptor-dependent) is not found in any of Applicants cited passages which are limited to alternative means of receptor-independent delivery or specifically relate to only description of receptor-independent transport peptides. Applicants have not pointed to any passage that does not relate to the transport peptide as being receptor dependent. Each passage recites and is directed to receptor-independent transport peptides. There is no conception of the genus now claimed.

The rejection is maintained.

New Rejections Based on Amendment

Claims 1, 4, 12, 16, 19, 20, 22, 23, 45-49, 51-56 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is a new matter rejection.

As to claims 1, 4, 12, 16, 19, 20, 22, 23, 45-46, 48-49, 51-56, the claims now generically recites that the exogenous dominant negative phospholamban functionally attached to a "vesicle based transfer system". While the specification at page 23 and original claim 7 provide for lipid-vesicle based transfer system, the specification as filed does not provide conception by way of written description for vesicle-based delivery systems in general. Vesicles can be made from numerous different types of molecules. These molecules include non-lipid moieties, such as surfactants or proteins or a combination based thereon. The specification only supports conception for a lipid-vesicle based transfer system. To satisfy the written description requirement, an applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, applicant was in possession of the invention and that the invention, in that context, is whatever is now claimed. See MPEP 2163.02. Also, the failure to meet the written description requirement under 35 USC 112, first paragraph arises when the claims are changed after the filing date to change the scope of the disclosure. In the instant case, the specification as filed provided no written description of these other vesicle-based delivery systems and therefore has no conception of the now broadly claimed vesicle-based delivery systems. As to claim 51, an adenovirus virion is not a vesicle per se. It is a non-enveloped virus. As to claim 52, the claim creates a new subgenus of bacterial and lipid-vesicle based transport peptide. The specification teaches transport peptides and

generic lipid vesicle based transport. The specification as filed does not provide conception of the now claimed subgenus of a bacterial or lipid based transport peptide. These issues are best resolved by Applicants pointing to the specification to provide conception by way of written description for the now claimed genus of vesicles and the new subgenera as now claimed..

As to claims 46 and 47, the claims recite the concept of "increasing heart activity". Increasing heart activity lacks explicit written description in the specification as originally filed. The specification supports treatment of cardiac disease and heart failure and increasing cardiac contractility. The concept of enhancing cardiac contractility is the force of contraction of the heart muscle. It does not support conception by way of written description of "increasing heart activity" because this concept includes increasing the number of heartbeats, regulating heartbeat, restoring a heartbeat, treating miss-functioning valves, increasing ejection fraction volume etc. As such, the concept of increasing cardiac contractility does not support conception of increasing heart activity in general. The specification as filed does not support the concept as now broadly claimed.

Claims 49 and 52-56 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

As to claim 49, the claim recites that the transport peptide comprises a receptor-independent mechanism. A structural element cannot comprise a mechanism. As such, the metes and bounds of the transport peptide cannot be ascertained.

As to claim 52, the specification does not teach a bacterial and a lipid-based transport peptide. As such, the skilled artisan would not be readily apprised of the metes and bounds of these transport peptides.

AS to claims 53-56, the claims recite specific mutations as specific positions. Positions in any sequence are relative. These claims are prima facie indefinite in the

absence of a reference sequence identifier, because it is unclear what positions are referenced in the absence of a corresponding reference sequence that places the recited residues in context of a particular reference sequence.

Status of Claims

Claims 24-39 are withdrawn from consideration. Claims 1, 4, 12, 16, 19, 20, 22, 23, 40-56 stand rejected.

Conclusion

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL.** See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Patricia A. Duffy whose telephone number is 571-272-0855. The examiner can generally be reached on M-Th 6:30 am - 6:00 pm. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Lynette Smith can be reached on 571-272-0864.

The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Patricia A. Duffy
Primary Examiner
Art Unit 1645